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INVESTIGATING TOBACCO WITHDRAWAL IN OPIOID-MAINTAINED SMOKERS AND SMOKERS WITH OTHER VULNERABILITIES

A Dissertation Presented

by

Joanna M. Streck

to

The Faculty of the Graduate College

of

The University of Vermont

In Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy
Specializing in Psychology

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ABSTRACT

While smoking rates in the general adult population have declined, smoking remains entrenched among individuals with opioid use disorder (OUD). Individuals with OUD have an extremely high prevalence of smoking, experience poor cessation outcomes, and bear a disproportionate burden of smoking-related adverse health consequences. Data have also suggested that opioid-maintained (OM) smokers may experience a unique response to nicotine including heightened reinforcement and potentially more severe withdrawal when stopping smoking. Thus, this is a sub-group of smokers for which novel harm reduction paradigms are urgently needed to reduce the burden of smoking. A promising national policy is currently under consideration by the Food and Drug Administration to decrease the nicotine content of cigarettes in an effort to reduce smoking prevalence and smoking-related disease. It is critical to understand the extent to which reduced nicotine content cigarettes (RNCCs) can attenuate tobacco withdrawal severity in OM smokers as this has direct implications for the potential acceptability and uptake of reduced nicotine cigarettes in this vulnerable subgroup.

The primary aims of this study were to rigorously examine the effects of OM status on tobacco withdrawal and craving in response to participants' usual brand cigarette and research cigarettes that varied in nicotine content. Opioid-maintained (OM; n=65) vs. non opioid-maintained (NOM; n=135) smokers completed 5 outpatient laboratory sessions in which they smoked a single research cigarette varying in nicotine content (0.4, 2.4, 5.2, 15.8 mg/g of tobacco) or their usual brand cigarette under double-blind, acute abstinence conditions. Participants completed the Minnesota Tobacco Withdrawal Scale before and every 15 minutes for one hour following smoking each cigarette. As an exploratory aim, we also examined the contribution of OM status to tobacco withdrawal in the context of several other important characteristics associated with smoking vulnerability (e.g., depression, anxiety, education level). Repeated measures mixed model analyses were used to examine all aims.

Across usual brand cigarettes and RNCCs, tobacco withdrawal and craving did not differ as a function of OM status (*p's* >.05). In multivariable models, nicotine dose, time, depression, cigarette dependence, education level, but not OM status, consistently predicted tobacco withdrawal and craving severity (*p's* <.05). In particular, depression severity, rather than OM status, was the strongest and most consistent predictor of withdrawal and craving severity among the characteristics examined.

Despite prior data suggesting that OM smokers may respond differently to nicotine and experience more severe withdrawal during reductions in nicotine intake, OM smokers in this study responded favorably to RNCCs. These findings provide additional support for the potential beneficial effects of a national nicotine reduction policy for reducing the burden of smoking and smoking-related consequences among smokers with concurrent OUD.

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CHAPTER 1: INTRODUCTION

1.1. Cigarette Smoking Among Individuals with Opioid Use Disorder

Despite considerable progress in tobacco control and prevention, cigarette smoking remains the leading cause of preventable death and disability in the United States (US) and is responsible for nearly 500,000 deaths each year (US Department of Health and Human Services, 2014). While the prevalence of smoking among the general US adult population has declined over the past several decades, it remains entrenched among certain vulnerable populations. This is especially the case among individuals with co-morbid substance use disorders (SUDs), non-SUD psychiatric disorders and socioeconomic disadvantage, all of whom are overrepresented among current cigarette smokers and bear a disproportionate burden of smoking-related disease (Hiscock, Bauld, Amos, Fidler, & Munafò, 2012; Schroeder & Morris, 2010). For example, while smoking prevalence has markedly decreased among individuals without SUDs, recent nationally-representative data suggests that the prevalence of cigarette smoking in the US is actually increasing among those with SUDs, excluding cannabis use disorders (Weinberger et al., 2018).

Individuals with opioid use disorder (OUD) represent a population that is particularly vulnerable to cigarette smoking and its adverse health effects. Prevalence of smoking in this group is up to six-fold higher than the general population (84-94% vs. 15%, respectively)(Guydish et al., 2011, 2016; Hser, Hoffman, Grella, & Anglin, 2001; Hser et al., 1994; Jamal, 2016; Nahvi, Richter, Li, Modali, & Arnsten, 2006; Richter, Gibson, Ahluwalia, & Schmelzle, 2001), and the incidence of all-cause mortality is four-fold that of nonsmokers with OUD (Hser et al., 1994). Prevalence of smoking is also

higher among individuals in treatment for OUD compared to other SUDs (Guydish et al., 2016, 2011). Finally, individuals with OUD often present with additional risk factors that may further increase their risk for smoking and related adverse consequences, including increased prevalence of comorbid non-SUD psychiatric disorders (e.g., depression and personality disorders) and socioeconomic disadvantage (e.g., limited educational attainment), both of which are independently associated with increased prevalence rates of smoking and poorer cessation outcomes (e.g., Higgins & Chilcoat, 2009; Hiscock et al., 2012; Kurti et al., 2016; Lasser et al., 2000).

Most individuals with OUD are aware of the health risks of smoking, express an interest in quitting, and express interest in receiving smoking cessation services (Clarke, Stein, McGarry, & Gogineni, 2001; Clemmey, Brooner, Chutuape, Kidorf, & Stitzer, 1997; Dunn, Sigmon, Reimann, Heil, & Higgins, 2009; Frosch, Shoptaw, Jarvik, Rawson, & Ling, 1998; Kozlowski, Skinner, Kent, & Pope, 1989; Nahvi et al., 2006; Richter et al., 2001; Sees & Clark, 1993). Despite this, responses to smoking cessation interventions are notoriously poor in this group, with abstinence outcomes one-fourth that of non-substance abusing smokers (Miller & Sigmon, 2015; Okoli et al., 2010; Zirakzadeh, Shuman, Stauter, Hays, & Ebbert, 2013) and standard first-line pharmacotherapies largely ineffective (Dunn et al., 2010; Miller & Sigmon, 2015; Okoli et al., 2010; Zirakzadeh et al., 2013).

1.2. Nicotine Dependence in Smokers with OUD

While the specific factors contributing to the elevated smoking prevalence and poor cessation outcomes among individuals with OUD are not well understood, one

possibility is that smokers with concurrent SUDs may present with more severe nicotine dependence than smokers without co-occurring SUDs. Nicotine dependence (referred to as tobacco use disorder in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)) is characterized by tolerance, withdrawal and craving for nicotine during abstinence, and loss of control over the amount or duration of use (American Psychiatric Association, 2013).

Rates of nicotine dependence are two to four times higher in adults with current SUDs compared to the general population (Grant, Hasin, Chou, Stinson, & Dawson, 2004). However, there is little research investigating nicotine dependence severity among individuals with OUD specifically. We recently examined associations between OUD and nicotine dependence using nationally representative cross-sectional data from the National Survey on Drug Use and Health (Parker, Streck, & Sigmon, 2018). After adjusting for baseline characteristics, adult daily smokers with OUD were roughly twice as likely to be dependent on nicotine as compared to those without OUD. Smokers with OUD also evidenced a greater severity of nicotine dependence compared to those without OUD as measured by the Nicotine Dependence Severity Scale (NDSS; Shiffman, Waters, & Hickcox, 2004). Importantly, greater baseline severity of nicotine dependence has been shown to predict poorer cessation outcomes in the general smoker population (Borland, Yong, O'Connor, Hyland, & Thompson, 2010; Breslau, Johnson, Hiripi, & Kessler, 2001; Fagerstrom & Schneider, 1989; Kozlowski, Porter, Orleans, Pope, & Heatherton, 1994; Transdisciplinary Tobacco Use Research Center et al., 2007; Vangeli, Stapleton, Smit, Borland, & West, 2011).

1.3. Tobacco Withdrawal in Smokers with OUD

Tobacco withdrawal, a hallmark feature of nicotine dependence, may also play a role in opioid-dependent individuals' smoking behavior. Given the high rates of smoking, nicotine dependence and poor cessation outcomes in this population, for example, one might expect to find elevated withdrawal severity upon discontinuation of smoking. In the general smoker population, individuals who experience greater withdrawal upon quitting smoking are at increased risk for relapse (Allen, Bade, Hatsukami, & Center, 2008; American Psychiatric Association, 2013; Hughes, 2007a; Patten & Martin, 1996; West, Hajek, & Belcher, 1989).

The extant data do suggest elevated incidence and severity of tobacco withdrawal among smokers with concurrent SUDs (Breslau, Kilbey, & Andreski, 1992; Hughes, 1996; Weinberger, Desai, & McKee, 2010). However, there is a paucity of empirical data on tobacco withdrawal among smokers with OUD, and the limited studies thus far have produced mixed results. To our knowledge, only three published studies have evaluated tobacco withdrawal among smokers receiving methadone or buprenorphine maintenance for treatment of OUD. In an early report on this topic, Story and Stark (1991) examined the efficacy of a methadone dose increase as a pharmacological adjunct to a cognitive-behavioral treatment for smoking cessation. Methadone-maintained participants (n=33) were randomly assigned to either an experimental group which received a 20% methadone dose increase for a 28-day experimental period or to a control group that received a one milligram dose increase for the same duration. There were no significant differences between experimental groups in cigarette abstinence rates, though participants receiving the methadone dose increase did report more tobacco withdrawal

symptoms than controls. However, the findings were limited by a sizeable amount of continued smoking in both experimental groups.

In a more recent study, Elkader and colleagues examined methadone and nicotine interactions among methadone-maintained patients (n=40) during trough and peak methadone dose conditions using a within-subject design (Elkader, Brands, Selby, & Sproule, 2009). Participants rated their tobacco withdrawal symptoms before and after self-administering nicotine (own-brand cigarettes, nicotine gum or placebo gum, depending on the study day) following 12 hours of smoking abstinence under two methadone dosing conditions: Before they ingested their daily methadone dose (at trough methadone blood levels) and 3 hours following methadone administration (peak methadone blood levels). In that study, there was a main effect of methadone dose condition on tobacco withdrawal severity, whereby tobacco withdrawal was attenuated when methadone was at peak (vs. trough) levels.

Finally, we recently examined the timecourse and severity of tobacco withdrawal among methadone- or buprenorphine-maintained (n=47) vs. non-SUD smokers (n=25), all of whom completed one of several two-week studies involving daily visits for biochemical monitoring and delivery of financial incentives contingent on smoking abstinence (Streck, Heil, Higgins, Bunn, & Sigmon, 2018). To prevent ongoing smoking from confounding evaluations of withdrawal, we examined withdrawal severity among the subset of participants who achieved biochemically-verified smoking abstinence. While opioid-maintained smokers presented with significantly higher levels of withdrawal at study intake (when smoking as usual) relative to the non-SUD smokers,

the two groups had remarkably similar profiles of withdrawal across the two-week period of smoking abstinence.

In summary, while tobacco withdrawal severity is associated with relapse to smoking and is an important component of continued addiction to cigarettes in the general smoker population (Allen et al., 2008; Patkar, Vergare, Batra, Weinstein, & Leone, 2003; West et al., 1989), its potential role among smokers with OUD remains unclear. Of the three studies that have examined withdrawal among opioid-dependent smokers, one suggested that opioid agonists may be associated with more severe withdrawal, one suggested that opioids may attenuate withdrawal, and one found no difference in withdrawal between opioid-dependent and non opioid-dependent smokers. The methodological differences across these studies may account for these mixed findings, as they employed different scientific designs and analytic approaches (e.g., within-subject vs. cross-sectional designs, evaluating withdrawal only among abstinent vs. all smokers, evaluating smoking during stable vs. acute changes in opioid dose). Further, none of the prior studies utilized double-blind nicotine administration or examined multiple nicotine doses, and all generally focused on withdrawal following abrupt discontinuation of smoking.

1.4. Reducing the Nicotine Content of Cigarettes

There is an urgent need to understand the severity of withdrawal experienced by vulnerable smokers under conditions of reduced nicotine intake. A national policy is currently under consideration to reduce smoking prevalence and smoking-related disease in the US by decreasing the nicotine content of cigarettes below the threshold necessary

to establish and sustain nicotine dependence (Benowitz & Henningfield, 1994; Gottlieb & Zeller, 2017). The 2009 Family Smoking Prevention and Tobacco Control Act granted the US Food and Drug Administration (FDA) regulatory authority over cigarettes and other tobacco products (111th Congress, 2009). That legislation includes the authority to reduce the maximal nicotine content of cigarettes, though not completely eliminate nicotine, if doing so benefits public health. This policy is based on the overwhelming scientific evidence that nicotine is the constituent in cigarette smoke that promotes repeated use and eventual addiction (Stolerman & Jarvis, 1995; US Department of Health and Human Services, 2014) and the decades of research demonstrating that reducing the amount of nicotine in cigarettes reduces their addiction potential (Benowitz & Henningfield, 2013; Boren, Stitzer, & Henningfield, 1990; Shahan, Bickel, Madden, & Badger, 1999). Thus, reductions in nicotine content may reduce smoking prevalence and related disease by disrupting initiation of smoking by new users and increasing cessation rates among current smokers. Well-controlled studies have demonstrated that use of reduced nicotine content cigarettes (RNCCs) in the general smoker population is associated with reductions in smoking rates, nicotine exposure, dependence and toxicant exposure, as well as increases in smoking abstinence (Benowitz et al., 2007, 2009; Donny, Houtsmuller, & Stitzer, 2007; Donny et al., 2015; Hatsukami, Hertsgaard et al., 2013; Hatsukami, Kotlyar et al., 2010). Further, in a recently published report, simulation modeling was used to estimate the effect of a national nicotine reduction policy on the prevalence of tobacco use, tobacco-related mortality and life-years gained (Apelberg et al., 2018). Not only would lowering the nicotine content of cigarettes lead to substantial reductions in tobacco use and smoking-related mortality, but the authors

projected that such a policy would result in 5 million additional adult smokers quitting smoking by 2020.

While these data are promising, the prior studies on RNCCs have excluded individuals with SUDs and non-SUD psychiatric disorders and instead focused on stable, generally "healthy" smokers. Considering their suboptimal response to standard smoking cessation treatments and substantial burden experienced from smoking, it is important to understand whether smokers with concurrent SUDs or other vulnerabilities may respond differently to RNCCs. Indeed, the US FDA's Center for Tobacco Products has identified these smokers as a priority population in whom more tobacco regulatory research is needed (US Department of Health and Human Services, 2017). With regard to opioid-dependent smokers specifically, given the scientific evidence that opioid agonist medications may increase the reinforcing effects of nicotine administration (Chait & Griffiths, 1984; Mello, Lukas, & Mendelson, 1985; Mello, Mendelson, Sellers, & Kuehnle, 1980), it is critical to ensure that these smokers will not compensate for reduced nicotine levels by increasing their smoking rates or experience a unique profile of subjective effects following use of RNCCs. Tobacco withdrawal is a subjective effect with direct implications for the potential acceptability and safety of RNCCs among consumers (Donny et al., 2014). While promising data suggest that RNCCs may attenuate tobacco withdrawal severity (Table 1), very little is known about the ability of RNCCs to attenuate tobacco withdrawal severity in smokers with co-occurring other vulnerabilities including OUD.

1.5. Evaluating RNCCs among Vulnerable Smokers

To our knowledge, only two studies have evaluated tobacco withdrawal among vulnerable smoker populations and only one of those included participants with SUDs. In an initial small, within-subject study, the effects of smoking a reduced nicotine cigarette, nicotine replacement therapy, and a usual brand cigarette were examined among individuals with schizophrenia (n=30) versus those without a psychiatric disorder (n=26) (Tidey, Rohsenow, Kaplan, Swift, & Ahnallen, 2013). While participants with schizophrenia reported greater tobacco withdrawal severity compared to those without psychiatric disorders across all study conditions, the RNCC was as effective at attenuating tobacco withdrawal symptoms as participants' usual brand cigarette.

The second and more recent study was completed by our research group (Higgins et al., 2017). To our knowledge, this has been the only trial to date to examine the acute effects of cigarettes varying in nicotine content among opioid-maintained smokers. Using a multi-site, double-blind, within-subject design, we sought to investigate the acute effects of RNCCs among three populations of vulnerable smokers (N=169): opioid-maintained individuals (n=60), individuals with affective disorders (n=56), and socioeconomically-disadvantaged women of childbearing age (n=53). Across 14 outpatient laboratory sessions, participants were acutely exposed to research cigarettes containing nicotine doses that ranged from levels below the proposed addiction threshold (Benowitz & Henningfield, 1994) to those consistent with commercially available cigarettes (i.e., 0.4, 2.4, 5.2, and 15.8 mg/g of tobacco), as well as to their usual brand cigarette. All study sessions were conducted following a brief period of smoking

abstinence (approximately 6-8 hours of abstinence or breath carbon monoxide levels ≤50% of baseline).

The relative reinforcing effects of smoking (i.e., addiction potential) decreased as an orderly function of decreasing the nicotine content of cigarettes in all three vulnerable populations. In terms of the withdrawal severity experienced and, importantly, the extent to which RNCCs attenuated smokers' withdrawal following acute abstinence, all nicotine doses significantly reduced tobacco withdrawal severity, with higher magnitude reductions seen at the higher dose cigarettes.

The primary outcomes in that study (e.g., reinforcing efficacy as evaluated by concurrent choice preference testing and behavioral economic simulation tests, compensatory smoking) were reported in aggregate across the vulnerable smoker sub-groups examined given the similarities among smoker groups on those measures. With regard to withdrawal, while opioid-maintained smokers reported levels of tobacco withdrawal that were higher than the socioeconomically-disadvantaged women and similar to smokers with affective disorders, how tobacco withdrawal severity changed over time among opioid-maintained (OM) smokers and whether there were differences in withdrawal as a function of the nicotine doses were not examined. Additionally, how the other characteristics representative of vulnerability to smoking (e.g., depression, educational attainment) may affect withdrawal severity and contribute to OM smokers' response to the cigarettes in this trial has not been evaluated.

1.6. Aims/Hypotheses

We sought to comprehensively evaluate tobacco withdrawal severity in response to acute exposure to RNCCs among OM smokers under conditions of double-blind nicotine administration, acute abstinence and across multiple nicotine doses. Our overarching aim was to better understand the ability of cigarettes varying in nicotine content to attenuate tobacco withdrawal severity in OM compared to non opioid-maintained (NOM) smokers.

In Aim 1, we examined the association between OM status (i.e., opioid-maintained participants vs. all other study participants) and tobacco withdrawal in response to participants' usual brand cigarette. We hypothesized that OM smokers would experience greater severity of tobacco withdrawal than NOM smokers.

In Aim 2, we examined the association between OM status and tobacco withdrawal in response to the four research cigarette doses (0.4, 2.4, 5.2, 15.8 mg/g) under double-blind conditions. We hypothesized that OM status would moderate the relationship between nicotine dose and withdrawal severity. Specifically, we anticipated that higher nicotine dose research cigarettes would reduce tobacco withdrawal severity to a greater extent among NOM smokers vs. OM smokers.

As an exploratory Aim 3, we also examined the contribution of other characteristics previously associated with smoking vulnerability (e.g., depression, anxiety, education level) on acute withdrawal in response to cigarettes varying in nicotine content, as well as how each vulnerability was associated with tobacco withdrawal over and above OM status. This research question stemmed in part from the previously-discussed observation of sub-group differences in tobacco withdrawal severity in the

parent trial in which more severe withdrawal was seen among OM smokers and those with affective disorders relative to disadvantaged women (Higgins et al., 2017) (Figure 1), suggesting that project-specific inclusion criteria such as anxiety, depression and education level were particularly important to consider. It also drew from the larger literature showing that non-SUD psychiatric disorders (e.g., mood, anxiety, personality disorders) and socioeconomic disadvantage (e.g., level of educational attainment) are not only independently associated with elevated smoking prevalence and lower quit rates compared to the general population, but also co-occur at high rates in populations with OUD (Higgins, 2016; Higgins & Chilcoat, 2009; Hiscock et al., 2012; Lasser et al., 2000; Parsells, Kelly et al., 2008; SAMHSA, 2015; Schroeder, 2016; Strain, 2002; US Department of Health and Human Services, 2014). Further, relevant to tobacco withdrawal specifically, there is strong evidence in the literature that non-SUD psychiatric disorders are associated with a greater incidence and severity of tobacco withdrawal (Covey, Glassman, & Stetner, 1990; Morrell, Cohen, & al'Absi, 2008; Pomerleau, Marks, & Pomerleau, 2000; Smith, Homish, Giovino, & Kozlowski, 2014; Weinberger et al., 2010). Emerging research has also suggested that this pattern of elevated withdrawal severity may extend to those with socioeconomic disadvantage (Harwood, Salsberry, Ferketich, & Wewers, 2007; Hiscock et al., 2012; Marmot & Wilkinson, 2005; Wiltshire, Bancroft, Parry, & Amos, 2003). Considering the potential synergistic interaction among risk factors that may influence tobacco withdrawal severity in OM smokers, in Aim 3, we examined how OM status may contribute to withdrawal in the larger context of other smoking-related vulnerabilities that so often co-occur in

opioid-dependent smokers. As this represented an exploratory aim, we did not propose a directional hypothesis for this outcome.

1.7. Summary

Taken together, we are at a critical moment in tobacco regulatory science and tobacco control with the FDA actively considering reducing the nicotine levels of cigarettes as a national harm reduction policy. Scientific efforts are urgently needed to understand the impact of such a nicotine reduction policy on the populations of smokers with co-occurring vulnerabilities that smoke the majority of the cigarettes in the US (Lasser et al., 2000). An improved understanding of the ability of reduced nicotine cigarettes to attenuate tobacco withdrawal in opioid-maintained smokers stands to directly inform FDA policy decisions and advance efforts to reduce the disproportionate burden of smoking in this population.

CHAPTER 2: METHODS

2.1. Participants

Participants were 202 daily smokers (65 with affective disorders, 66 with OUD, 71 socioeconomically-disadvantaged women). Participants were recruited though advertisements placed on Facebook, bulletin boards throughout the community, buses and local newspapers at Johns Hopkins University, Brown University and the University of Vermont. The study was approved by the respective universities' Institutional Review Boards, and all participants provided written informed consent. Parent study inclusion criteria required that participants were ≥18 years of age, reported smoking ≥5 cigarettes per day for the past year and provided an expired breath carbon monoxide (CO) level of >8 particles per million (ppm). All participants had to provide a negative urine toxicology test for illicit drugs other than marijuana. Exclusion criteria included an intention to quit smoking within the next 30 days, significant use (>9 days) of other tobacco products in the past 30 days, currently pregnant or trying to become pregnant, breastfeeding, exclusive use of "roll your own" cigarettes, or current suicidal ideation or a recent suicide attempt.

Additionally, there were several additional project-specific inclusion (Figure 2) and exclusion criteria. Participants in the OM smokers project were females and males ages 18-70 who were currently receiving methadone or buprenorphine maintenance treatment. They were required to be stable on their maintenance dose which was defined as no change in dose and <30% urine toxicology samples testing positive for illicit drug use in the past month. Participants in the affective disorders project were females and males ages 18-70 years who met criteria for current or past year major depressive

disorder, dysthymic disorder, generalized anxiety disorder, post-traumatic stress disorder, obsessive compulsive disorder, specific phobia or panic disorder with or without agoraphobia based on the MINI International Neuropsychiatric Interview for DSM-IV (Sheehan et al., 1998). Finally, participants in the project with socioeconomically-disadvantaged women were females, ages 18-44, with less than an associate's degree.

2.2. Research Cigarettes

Research cigarettes were manufactured by the 22nd Century Group (Clarence, NY) and included four nicotine content dose conditions: 0.4, 2.4, 5.2, and 15.8 milligrams of nicotine per gram (mg/g) of tobacco (Donny et al., 2015; Higgins et al., 2017). The research cigarettes were identical in appearance to one another and to commercially-available cigarettes but varied in nicotine content. The 15.8 mg/g cigarette was designed to have a nicotine content similar to commercially available cigarettes, the 0.4 mg/g cigarette fell below the hypothesized threshold of addiction (Benowitz & Henningfield, 1994), and the 5.2 and 2.4 mg/g cigarettes represented reduced nicotine content cigarettes. All sessions involving research cigarettes took place under double-blind conditions with each cigarette dose being represented by a letter code for blinded research staff.

2.3. Procedures

The parent study consisted of 14 experimental sessions using a within-subject design. All sessions were conducted under conditions of brief smoking abstinence

(breath CO≤50% of baseline). Participants were instructed to abstain from smoking for at least six to eight hours prior to the session so as to meet the breath CO criteria. At the start of each session, participants took two puffs from their usual brand cigarette in order to equate the time since last cigarette across study participants (Henningfield & Griffiths, 1981). Thirty minutes following the two puffs marked the beginning of the experimental session. During this 30-minute break participants completed the Minnesota Tobacco Withdrawal Scale (MTWS; Hughes & Hatsukami, 1986; described in greater detail below) and the Questionnaire on Smoking Urges-Brief (QSU; Cox, Tiffany, & Christen, 2001) to assess baseline levels of tobacco withdrawal and craving, respectively, prior to exposure to the research cigarettes. The 14 study sessions were divided into three study phases. As Phase 1 is the focus of this project, Phases 2 and 3 will only be described briefly here (Higgins et al., 2017).

Study Intake Visit (Session 0). Participants presented for an in-person screening visit to determine their eligibility. Intake screening measures relevant to this dissertation included smoking and demographic characteristics (e.g., average cigarettes smoked per day, cigarette dependence severity, education level, gender, age). The Fagerström Test for Cigarette Dependence (FTCD) is a 7-item measure to assess cigarette dependence with total scores reported as the sum of scores on the first 6 items of the measure (Fagerström, 2012). Higher scores are suggestive of higher levels of dependence. The Beck Depression Inventory (BDI; Beck, 1996) and the Overall Anxiety Severity and Impairment Scale (OASIS; Norman, Cissell, Means-Christensen, & Stein, 2006) were used to assess depression and anxiety, respectively. The BDI is a 21-item measure which screens for depression severity in the past two weeks. Items are rated on a 0-3 scale with

total scores ranging from 0 to 63. A total score is computed based on summing scores on all items of the measure. Research suggests that a valid BDI cut-off to use in the research setting is a score of 17 or greater which is indicative of clinically meaningful depression and a potential need for treatment (Beck, 1996; Sprinkle et al., 2002). The OASIS is a 5-item screening measure assessing anxiety severity in the past week. Items are rated on a 0-4 scale with total scores ranging from 0 to 20. Finally, OM smokers also provided additional information on their opioid maintenance medication (e.g., methadone or buprenorphine, current dose).

Baseline Session (Session 1) and Study Phase 1 (Experimental Sessions 2-5).

Session 1 (i.e., baseline session) served as an orientation or practice session wherein participants smoked their usual brand cigarette using the study procedures that would be in place for remaining sessions. Thereafter during Sessions 2-5, participants sampled each research cigarette under double-blind, acute abstinence conditions with cigarettes presented in a random order (Figure 3). Participants smoked one of the four research cigarettes per session in a random order. In all sessions, participants were instructed to smoke the research cigarettes as they would smoke their usual brand cigarette, but to do so through a plastic cigarette holder connected to a device that recorded measures of smoking topography (Lee, Malson, Waters, Moolchan, & Pickworth, 2003).

After smoking the cigarette, participants then completed a battery of self-reported measures including the Cigarette Purchase Task (CPT; MacKillop et al., 2008), Modified Cigarette Evaluation Questionnaire (mCEQ; Cappelleri et al., 2007), QSU and MTWS, which measure hypothetical cigarette purchasing behavior, the degree to which people

experience the reinforcing effects of cigarettes, cigarette craving and tobacco withdrawal, respectively. The MTWS and the QSU were administered to participants every 15 minutes for an hour following the completion of the research cigarette in each session. At each 15-minute timepoint, research staff also measured expired breath CO levels using a hand-held device (CoVita, Haddonfield, NJ).

Study Phases 2 and 3. As noted above, Phases 2 and 3 were not a focus of this dissertation and thus are only briefly described here. During Phase 2 (Sessions 6-11), the relative reinforcing effects of the range of nicotine doses were evaluated using a concurrent choice testing paradigm, in which participants were instructed to choose which cigarette they preferred to smoke when both cigarettes were available at an equal response cost. In Phase 3 (Sessions 12-14), participants chose between cigarette dose pairs, with a focus on the highest and the lowest dose cigarettes. The highest dose cigarette had a higher response cost and was available on an increasing progressive ratio schedule.

2.4. Outcome Measures

The primary outcome measure was the Minnesota Tobacco Withdrawal Scale (MTWS; Hughes & Hatsukami, 1986), a 15-item self-report measure of tobacco withdrawal. Each item is rated on a 5-point ordinal scale (0=none, 1=slight, 2=mild, 3=moderate, 4=severe). The MTWS includes seven DSM-5 items (anger/irritability/ frustration, anxiety/nervousness, difficulty concentrating, impatience/restlessness, increased appetite/hunger, insomnia/awakening at night, depressed mood/sad) that are averaged to construct a single withdrawal severity score (i.e., MTWS Total score).

Additionally, a Desire to Smoke item is typically analyzed separately as a measure of craving (Hughes & Hatsukami, 1998). The scientific literature supports the reliability and validity of the MTWS in measuring withdrawal and craving severity in the general smoker population (Cappelleri et al., 2005; Etter & Hughes, 2006; Hughes, 2007; Javitz, Lerman, & Swan, 2012; Piper, 2015; Piper, McCarthy, & Baker, 2006; Toll, O'Malley, McKee, Salovey, & Krishnan-Sarin, 2007; Weinberger et al., 2007; West, Ussher, Evans, & Rashid, 2006).

During each session, the MTWS was administered following acute (i.e., 6-8 hours) abstinence and after taking the two puffs of the usual brand cigarette (Time 0; Pre-smoking baseline). MTWS administration was then repeated every 15 minutes for an hour following completion of the assigned research cigarette (Times 1-4). The dependent variables for this dissertation were the MTWS Total and Desire to Smoke scores across these five timepoints (Times 0-4) during the baseline session and Phase 1 of the study (Figure 3).

2.5. Statistical Analyses

This secondary analysis focused on participants who completed Phase 1 of the parent study (N=202). Of these, we excluded two participants as one participant had missing BDI and OASIS data from baseline and another participant had missing OASIS data at baseline (N=200). While one participant had missing MTWS data at a single timepoint for one session (45-minute point in Session 1), they were still included in the analyses.

Demographic, psychiatric and smoking characteristics were examined by OM

status using chi-square or Fisher's Exact tests for categorical variables and t-tests or Wilcoxon Rank Sum tests for continuous variables. To address Aim 1, MTWS Total scores and Desire to Smoke scores were examined during Session 1 (usual brand cigarette baseline session) using mixed-model repeated-measures (RM) analyses. Time (i.e., pre-smoking baseline and 15, 30, 45, and 60 minutes post-smoking the cigarette) was included in the model as a within-subject factor and OM status, dichotomized (yes vs no), was included as an across-subject factor. Study site was included as a random factor in this model.

For Aim 2, we similarly performed a mixed-model RM analysis. Time (i.e., pre-smoking baseline and 15, 30, 45, and 60 minutes after smoking the cigarette) and research cigarette dose (0.4, 2.4, 5.2, 15.8 mg/g) were included as within-subject factors and OM status as an across-subject factor. Study site was included as a random effect in this model.

In exploratory Aim 3, we examined the contribution of participant characteristics reflective of smoking vulnerability to tobacco withdrawal using multivariable mixed-model RM analyses. As with Aim 2, time and nicotine dose were within-subject factors and OM status was an across-subject factor. Variable selection for construction of the final model was based on both bivariate testing and the empirical literature. Age, race, gender, employment status, marital status, FTCD total score, cigarettes smoked per day, BDI and OASIS were included in preliminary models as there was evidence that they were associated with withdrawal based on bivariate testing ($p<.10$). Education level, age started smoking regularly and screening CO level were forced into preliminary models based on the literature. We chose to use a dichotomous variable for BDI in our models

for ease of interpretation using a commonly established cut-off of 17 to distinguish those with clinically meaningful depression levels (Beck, 1996; Sprinkle et al., 2002). Furthermore, in preliminary models, we forced OM status into models and added additional characteristics sequentially to determine how each was associated with tobacco withdrawal over and above OM status. We present final multivariable models in two ways: First, with only the variables that were significant predictors of tobacco withdrawal; second, with all significant predictors of withdrawal with OM status retained in the model, regardless of significance, as it was a main focus of the current study.

Finally, supplemental analyses were conducted to examine changes in withdrawal and craving in response to nicotine dose, using methods commonly employed in behavioral pharmacology research (e.g., Iversen & Lattal, 1991; Sobel, Sigmon, & Griffiths, 2004). First, we examined peak effects of the research cigarette nicotine doses' ability to attenuate withdrawal. Specifically, for Aims 1 and 2, we computed the peak change from baseline in withdrawal (i.e., difference between the pre-smoking baseline timepoint and the minimum withdrawal score seen between 15 and 60 minutes post-smoking) for each participant, then averaged across participants to form the dependent measure in mixed models. In these models, OM status was the primary independent variable and, for Aim 2, dose was also included in the model. Second, sensitivity analyses were conducted for Aims 2 and 3, examining area under the time curve (AUC) of repeated MTWS scores as the dependent variable to determine whether AUC analysis differs from repeated measures mixed modeling in explaining withdrawal scores over time. Finally, we compared data from participants who completed Phase 1 of the study

and were included in this secondary analysis (n=200) to those who dropped out (n=35) on our variables of interest to determine any potential biases due to attrition.

All post-hoc testing used a Bonferroni adjustment for multiple comparisons. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). Statistical significance was defined as $p<.05$.

CHAPTER 3: RESULTS

3.1. Participant Characteristics

Baseline demographic and smoking characteristics by OM status are presented in Table 2. Briefly, OM smokers were on average 41 years of age, 23% unemployed, smoked an average of 16 cigarettes per day and presented with an FTCD score of 5, suggesting moderate tobacco dependence. Compared to NOM smokers, OM smokers were older, less likely to be female, more likely to be nicotine dependent, and had lower levels of anxiety and depression. Employment and marital status were also significantly different between the groups.

3.2. Aim 1

Mean tobacco withdrawal severity scores (i.e., MTWS Total scores) during the baseline (usual brand cigarette) Session 1 did not differ as a function of OM status ($F(1, 185)=0.69$, $p=.41$; Figure 4, upper panel). There also was no evidence of an interaction between OM status and time on mean withdrawal scores during the baseline session ($F(4, 791)=1.48$, $p=.21$).

A similar pattern was seen with cigarette craving (i.e., the Desire to Smoke item of the MTWS). Craving severity following smoking the usual brand cigarette did not differ as a function of OM status ($F(1, 198)=0.19$, $p=.66$; Figure 4, lower panel), nor was there a significant interaction between OM status and time on reports of cigarette craving ($F(4, 791)=1.53$, $p=.19$).

For both withdrawal and craving, there was a significant main effect of time ($F(4, 795)=52.80$, $p<.001$; $F(4, 795)=62.82$, $p<.001$, respectively) with MTWS scores

decreasing 15 minutes after smoking the usual brand cigarette and then gradually increasing over time (i.e., across the remaining 45 minutes of the hour following smoking).

3.3. Aim 2

When examining tobacco withdrawal during exposure to cigarettes varying in nicotine content during Sessions 2-5, withdrawal severity did not differ as a function of OM status ($F(1, 175)=1.65$, $p=.20$; Figure 5, upper panel). There also was no significant interaction on the withdrawal outcome between OM status and nicotine dose ($F(3, 591)=2.15$, $p=.09$) or among OM status, time and nicotine dose ($F(19, 3146)=1.35$, $p=.14$).

Similarly, there was no main effect of OM status on craving ($F(1, 198)=2.76$, $p=.10$), no OM by nicotine dose interaction ($F(3, 591)=2.34$, $p=.07$), and no OM status by time by nicotine dose interaction ($F(19, 3146)=1.57$, $p=.06$)(Figure 5, lower panel).

Consistent with the parent trial report (Higgins et al., 2017), there were significant dose x time interactions on both withdrawal and craving severity in Phase 1 ($F(12, 2386)=3.00$, $p<.001$; $F(12, 2385)=6.42$, $p<.001$, respectively) with both outcomes decreasing over time following smoking the research cigarettes and then gradually returning to baseline levels over time, with higher magnitude reductions seen at higher dose cigarettes. Finally, there were also main effects of dose and time for both withdrawal and craving measures (MTWS Total score: Dose $F(3, 591)=4.5$, $p<.001$, time

F(4, 793)=83.62, p<.001; MTWS Desire to Smoke: Dose F(3, 591)=7.04, p<.001, time F(4, 793)=130.93, p<.001).

3.4. Exploratory Aim 3

In exploratory Aim 3, we examined the contribution of OM status in relation to other participant characteristics reflective of smoking vulnerability to tobacco withdrawal and craving. Regarding withdrawal during the baseline Session 1 (i.e., usual brand cigarette session), time, BDI and FTCD, but not OM status, were significantly associated with tobacco withdrawal severity (Table 3, upper right panel). In a final model that only included significant predictors of withdrawal severity, time, BDI score and FTCD total score were significant predictors in this usual brand cigarette session (Table 3, upper left panel). In these models, individuals with clinically meaningful depression (i.e., BDI total score $\geq$17) evidenced greater levels of withdrawal severity compared to those without clinically elevated depression (i.e., BDI total score <17) (mean difference=0.60; p<.001). Similarly, those with higher levels of baseline cigarette dependence as measured by the FTCD also evidenced greater withdrawal severity (β(SE) =0.06 (0.02), p<.01) in response to the usual brand cigarette.

During Sessions 2-5 evaluating research cigarettes with varying nicotine content, the significant predictors of withdrawal were nicotine dose, time, the dose x time interaction, BDI, education level, race, FTCD total score and OM status (Table 3, lower right panel). While OM status was a significant predictor of withdrawal in this model (F(1,191)=6.65; p=.01), it was subsequently dropped from the final model as there was evidence of confounding between OM status and BDI. Specifically, not only was OM

status not a significant predictor of withdrawal in any of the prior models, but there were significant correlations between BDI scores and OM status (Spearman correlation= -0.26, $p<.001$). With regards to differences by race, Non-Latino White participants had higher withdrawal than Non-Latino Black participants (mean difference=0.39; $p=0.01$). The resulting final model predicting withdrawal included nicotine dose, time, the dose x time interaction, BDI, FTCD scores, and education level (Table 3, lower left panel). In this model, higher depression at baseline (mean difference=0.64, $p<.001$) and higher cigarette dependence (β(SE)=0.07(0.02), $p<.01$) were predictive of greater tobacco withdrawal. Lower educational attainment (i.e., high school education vs. some college and some college vs. associate's degree or higher) also predicted greater withdrawal in response to the cigarettes varying in nicotine content (mean differences=0.29 and 0.33, respectively; p's<.05).

With regard to craving, time, BDI, FTCD and screening CO level, but not OM status, were significantly associated with craving during the baseline Session 1 (i.e., usual brand cigarette session) (Table 4, upper right panel). The final model of variables significantly predicting craving during this session included time, BDI, FTCD and screening breath CO level (Table 4, upper left panel). Higher baseline levels of depression (mean difference=0.32, $p=0.01$), cigarette dependence (β(SE)=0.14 (0.03); $p<.001$) and breath CO levels at study intake (β(SE)=0.02 (0.01); $p<.01$) were predictive of greater craving severity.

Finally, in terms of craving during exposure to cigarettes varying in nicotine content, significant predictors of craving were nicotine dose, time, dose x time interaction, FTCD total score, the OM status x time interaction, but not OM status (Table

4, lower panel). The significant interaction between time and OM status was primarily driven by between-group differences in mean craving at the last time point (i.e., an hour after smoking the research cigarette) (adjusted means=2.95 vs. 2.63 for OM vs. NOM, respectively; p=.04); however, none of the comparisons of means at each timepoint between groups differed after Bonferroni adjustment (p's=1.0), suggesting that confounding of multiple comparisons may have driven the significant interaction seen in the final model.

3.5. Additional Analyses

As previously noted, several additional analyses were conducted to examine peak change from the pre-smoking baseline timepoint for withdrawal and craving in baseline Session 1 and across Sessions 2-5. We also examined AUC analyses to validate the results from mixed modeling. Finally, to address attrition, we compared those who did and did not complete Phase 1 on our variables of interest to determine any potential biases due to attrition.

When examining peak change from the pre-smoking baseline timepoint during baseline Session 1 (related to Aim 1), there were no differences by OM status for MTWS Total scores ($F(2, 197)=0.41$, p=.52) or Desire to Smoke ($F(2, 197)=0.06$, p=.81). A similar pattern was observed when examining peak change during Sessions 2-5 (related to Aim 2), with no differences by OM status for MTWS Total scores ($F(1, 198)=0.56$, p=.46) or Desire to Smoke ($F(1, 198)=0.11$, p=.75). There were main effects of nicotine dose on peak change in MTWS Total ($F(3, 595)=4.04$, p<.001) and Desire to Smoke

scores (F(3, 595)=14.17, p<.001), with higher nicotine doses resulting in a larger magnitude reduction in MTWS scores from the pre-smoking baseline timepoint.

Regarding AUC analyses across the multiple nicotine doses evaluated in Sessions 2-5, there was neither an effect of OM status (F(1, 171)=1.68, p=.20) nor an OM status by nicotine dose interaction (F(3, 587)=2.37, p=.07) on MTWS Total score AUC. There also were no main effects of OM status on Desire to Smoke AUC (F(1, 198)=2.61, p=.11), though there was a significant OM status by nicotine dose interaction (F(3, 587)=2.85, p=.04). Upon probing this interaction, we determined that it was primarily driven by between-group differences in mean craving AUC at the 5.2 mg/g cigarette (adjusted means=10.67 vs. 8.83 for OM vs. NOM, respectively; p=.01)(Figure 5); however, this difference was no longer significant after Bonferroni adjustment for multiple comparisons (p=.15). Thus, overall, AUC analyses produced similar results to the repeated measures mixed model analyses, with no robust effects of OM status on tobacco withdrawal or craving scores via the MTWS. In both models predicting tobacco withdrawal and craving AUC in Phase 1, there were main effects of nicotine dose (F(3, 587)=4.74, p<.01; F(3, 587)=8.73, p<.001, respectively) consistent with repeated measures mixed model analyses.

Additional analyses for exploratory Aim 3 used AUC to examine tobacco withdrawal and craving in the above multivariable models and produced similar results to repeated measures mixed modeling, again suggesting that OM status does not

contribute significantly to withdrawal or craving across usual brand cigarettes or cigarettes varying in nicotine content (Table 5).

Finally, our completer analysis suggested that individuals who did (n=200) vs. did not (n=35) complete Phase 1 were similar on nearly all demographic and smoking characteristics with the exception of higher cigarettes smoked per day reported at study intake among individuals who did not vs. did complete Phase 1 (means=18 vs. 15 average cigarettes/day, respectively; p=.05) (Table 6).

CHAPTER 4: DISCUSSION

4.1. Effects of Opioid Maintenance and Other Vulnerabilities on Tobacco Withdrawal

Smokers with concurrent opioid use disorder have an extremely high prevalence of smoking, experience poor cessation outcomes, and bear a disproportionate burden of smoking-related adverse health consequences. This is a subgroup of smokers for whom novel harm reduction paradigms are urgently needed to reduce the burden of smoking. A promising national policy is currently under consideration by the FDA to decrease the nicotine content of cigarettes in an effort to reduce smoking prevalence and smoking-related disease (111th Congress, 2009; Gottlieb & Zeller, 2017). However, data have suggested that OM smokers may experience a unique response to nicotine including heightened reinforcement and potentially more severe withdrawal when stopping smoking (Chait & Griffiths, 1984; Story & Stark, 1991; Weinberger et al., 2010). Thus, it is critical to understand the extent to which reduced nicotine cigarettes may attenuate tobacco withdrawal severity in this vulnerable smoker group as this has direct implications for the potential acceptability and uptake of reduced nicotine cigarettes in OM smokers.

Across usual brand and reduced nicotine cigarettes, tobacco withdrawal and craving did not differ as a function of OM status. While these results are inconsistent with our hypotheses that OM status would moderate the relationship between nicotine dose and withdrawal severity, they are consistent with our recent study examining tobacco withdrawal severity in OM vs. non-SUD smokers in which no differences in withdrawal or craving severity were observed between groups across a 2-week period of biochemically-verified smoking abstinence (Streck et al., 2018). Whereas the prior

investigation examined individuals who quit smoking their usual brand cigarettes for a 2-week study period, the current study further extends that work by including an evaluation of multiple nicotine doses, rigorous double-blind conditions, and smokers who were not currently interested in quitting smoking. The finding that OM smokers did not experience greater tobacco withdrawal or craving relative to other vulnerable populations without concurrent opioid dependence suggests that a national nicotine reduction policy would not produce untoward withdrawal-related effects in this important smoker group.

In exploratory analyses, we also examined several other characteristics reflective of smoking vulnerability (e.g., depression, nicotine dependence, educational attainment) and their contributions to tobacco withdrawal and craving severity. Generally, the strongest predictor of both withdrawal and craving was baseline depression, with clinically meaningful depression at study intake consistently associated with increased withdrawal and craving across all nicotine doses. Once again, OM status did not exert a meaningful influence on withdrawal or craving when accounting for other vulnerabilities. These findings are consistent with prior research showing elevated incidence and severity of tobacco withdrawal among smokers with affective disorders, particularly depression (Covey et al., 1990; Morrell et al., 2008; Pomerleau et al., 2000; Smith et al., 2014; Weinberger et al., 2010). Also worth noting is that negative affect is a strong contributor in both depression and tobacco withdrawal (Tonkin et al., 2018), and depressed mood/sadness is an item on the MTWS. Our data are also consistent with the only other prior study to our knowledge which has examined the effects of depressive symptoms on tobacco withdrawal in response to RNCCs (Tidey et al., 2017). In that study, which was conducted with generally healthy smokers, while there were no interactions between

nicotine dose and depression on withdrawal, greater withdrawal severity was observed across nicotine doses in participants with higher levels of depression. Overall, given the high rates of concomitant depression and other psychiatric disorders among OM patients (Barry et al., 2016; Kidorf et al., 2004; Strain, 2002), these findings may hold clinical significance for efforts to tackle smoking cessation among OM patients with co-occurring psychiatric distress. However, also important to note is that we did not see an additive effect on withdrawal severity of OM status and depression in this study. This is actually consistent with a prior report using nationally-representative data to examine the effects of having a co-morbid psychiatric disorder and SUD compared to a psychiatric disorder alone on tobacco withdrawal (Weinberger et al., 2010). In that study, while the presence of a SUD and a non-SUD psychiatric disorder were each independently associated with increased presence and severity of withdrawal symptoms, the two types of disorders did not act additively to increase withdrawal symptoms. That study did not examine the effects of OUD specifically.

Several comments are warranted on the other characteristics examined during the exploratory Aim 3 analyses. First, in the multivariable models, anxiety was not a final significant predictor of withdrawal once depression was added to the model. Prior studies have demonstrated an association between anxiety and increased incidence and severity of tobacco withdrawal (Breslau et al., 1992; Morrell et al., 2008; Weinberger et al., 2010; Zvolensky et al., 2008). It is possible that the instrument selected to measure anxiety in this study (i.e., OASIS) may have been less sensitive than those used in prior studies on this topic. For example, while the OASIS is a widely used and accepted screening measure for anxiety, the four studies above demonstrating a significant association between anxiety

and tobacco withdrawal used other measures (e.g., Anxiety Disorders Interview Schedule, National Institute of Mental Health Diagnostic Interview Schedule). Thus, it is possible that future studies evaluating anxiety and RNCC-associated withdrawal severity in OM smokers with other instruments may find a more robust association.

Second, lower educational attainment was associated with more severe tobacco withdrawal across nicotine doses. Limited educational attainment has been identified as an important proxy for socioeconomic disadvantage (Shavers, 2007) and is associated with increased prevalence of smoking and smoking-related adverse consequences (Agaku, King, Dube, & Centers for Disease Control and Prevention, 2014; Jamal, 2016; King, Dube, & Tynan, 2012). Several prior reports have hypothesized that withdrawal may be greater among those with socioeconomic disadvantage more generally (Harwood et al., 2007; Hiscock et al., 2012; Marmot & Wilkinson, 2005; Wiltshire et al., 2003), though we are aware of only two empirical investigations on this topic. In the first study, Breslau and colleagues examined epidemiological data from young adults in one state and found no effects of education level on tobacco withdrawal (Breslau et al., 1992). In the second, which was conducted in Syria, the authors reported that higher educational attainment was associated with lower withdrawal scores among patients enrolled in a smoking cessation trial (Ben Taleb et al., 2016). To our knowledge, the present study is the first to report on the potential role of educational attainment on tobacco withdrawal in response to RNCCs.

4.2. Limitations and Strengths

Several limitations of this study are important to note. First, we utilized an acute exposure paradigm wherein participants abstained from smoking for 6-8 hours (versus 12-hour abstinence or longer), sampled each dose research cigarette during one laboratory session, and rated their withdrawal across one hour post-smoking (versus days or weeks). As such, we did not examine the full timecourse of tobacco withdrawal during extended exposure, but rather the extent to which RNCCs may attenuate tobacco withdrawal severity under conditions of acute abstinence. These acute-exposure data support the feasibility of a national nicotine reduction policy in OM and other vulnerable populations. However, additional extended exposure studies are needed to determine if our results generalize to a longer timecourse of withdrawal under conditions of extended abstinence and prolonged exposure to these reduced nicotine cigarettes. We are positioned to contribute new information on this question in the near future as we have an extended exposure (i.e., 12-week) trial currently underway examining the longer-term effects of RNCCs in OM and other vulnerable smoker populations. A recent publication of a similar extended exposure trial in generally healthy smokers reported mild and temporary increases in certain withdrawal symptoms with the extended use of RNCCs (i.e., anger, irritability, frustration, increased appetite), but that these symptoms resolved by 6 weeks (Dermody et al., 2018). Our forthcoming experimental study will extend upon these prior findings to specifically address withdrawal in response to extended exposure to RNCCs among vulnerable smokers.

Second, to be eligible for the present study, participants were required to be stable in their opioid treatment, with limited opioid medication dose changes or illicit drug use.

It is possible that a less stable population with OUD, such as those not currently receiving treatment, may not respond as favorably to the RNCCs and that question merits further investigation. A large number of individuals with OUD are not currently enrolled in opioid treatment (Saloner & Karthikeyan, 2015), and one study has reported higher levels of nicotine dependence and less motivation to quit among smokers not in opioid maintenance treatment (and actively using intravenous opioids) compared to those receiving treatment (Clarke et al., 2001). As we observed a positive relationship between nicotine dependence and tobacco withdrawal in response to RNCCs, it is possible that smokers with OUD who are not stable in opioid treatment may experience greater withdrawal, though this is an empirical question that should be addressed more definitively in future studies.

Third, this was a secondary analysis of data from a study that was not originally designed or intended to examine outcomes as a function of OM status; that is, the participant sample that was recruited for the parent study did not involve equal numbers of OM and NOM smokers or comparable sociodemographic characteristics (e.g., gender) across OM groups. Although, we controlled for various sociodemographic characteristics that differed by OM status in multivariable analyses, that does not rule out the presence of other potential confounders. Additionally, as the parent trial was entirely focused on understanding RNCC response among smokers with concomitant vulnerabilities (e.g., anxiety/depression, socioeconomic disadvantage), there was no control group of 'healthy' smokers without these co-occurring factors in the present analyses.

This study also had several important strengths. First, this is the only study to date, to our knowledge, to rigorously evaluate tobacco withdrawal in response to RNCCs in OM smokers. Second, study methodology included a rigorous, double-blind, highly controlled design, multiple nicotine doses, availability of multiple empirically-supported measures reflecting vulnerability to smoking, and minimal missing data or attrition. Third, it also is the first study to investigate the separate and combined effects of multiple co-occurring vulnerabilities (e.g., opioid dependence, depression, anxiety, socioeconomic disadvantage) and their impact on tobacco withdrawal severity in response to RNCCs. Finally, this investigation is uniquely positioned to inform the FDA's decision making around reduced nicotine content cigarettes and their safety and acceptability in vulnerable smoker populations as it moves toward the potential implementation of a national nicotine reduction policy.

4.3. Conclusions

Despite prior data suggesting that OM smokers may respond differently to nicotine and experience more severe withdrawal during reductions in nicotine intake, opioid-maintained smokers in this study responded favorably to reduced nicotine content cigarettes. Specifically, under the conditions of acute exposure and abstinence evaluated, OM smokers did not experience more severe levels of tobacco withdrawal or craving relative to vulnerable smokers without concurrent opioid dependence. Depression severity, rather than opioid dependence, was the strongest and most consistent predictor of withdrawal and craving severity among the characteristics examined. These findings provide additional support for the potential beneficial effects of a national nicotine

reduction policy for reducing the burden of smoking and smoking-related consequences among smokers with concurrent opioid dependence.

Table 1

Prior Studies Examining Effects of Reduced Nicotine Content Cigarettes on Tobacco Withdrawal

Study	Sample	Methods	Tobacco Withdrawal Results
Benowitz et al., 2007	20 healthy adult smokers	10-week outpatient study, within-in subjects design, participants smoked usual brand and cigarettes with 12, 8, 4, 2 or 1 mg/g tobacco	Withdrawal increased during the nicotine taper from baseline to Week 6
Donny et al., 2007	30 healthy adult smokers	11-day inpatient study, between-subjects design, random assignment to cigarettes with 0.6 or, 0.05 mg of nicotine or a no smoking condition	No significant differences in withdrawal between the groups
Hatsukami et al., 2010	165 healthy adult smokers of light cigarettes	6-week outpatient study, between-subjects design, random assignment to 0.05 or 0.3 mg yield cigarettes or 4 mg nicotine lozenge	The 0.05 mg cigarette was associated with reduced withdrawal whereas 0.3 mg was associated with increased withdrawal vs. other products
Hatsukami et al., 2013	235 healthy adult smokers	6-week outpatient study, between-subjects design, random assignment to 0.05-0.09 mg nicotine yield cigarettes, 21 mg patch or 0.05-0.09 mg cigarettes with 21 mg patch, all groups received 6 weeks of behavioral treatment	Significant differences between groups with RNCCs+Patch group having lower withdrawal vs. Patch Alone
Donny et al., 2015	840 healthy adult smokers	6-week longitudinal outpatient study, between-subjects design, random assignment to usual brand cigarette or one of 6 types of research cigarettes ranging from 15.8 mg/g of tobacco to 0.4 mg/g	Cigarettes with 5.2 mg/g or less (vs. 15.8) did not significantly increase peak daily withdrawal during Weeks 1 or 6. Across the 6 weeks, there were no significant differences in withdrawal by dose.

Table 2

Baseline Demographic and Smoking Characteristics by Opioid-Maintenance Status

	All	Opioid-Maintained (OM)	Non Opioid-Maintained (NOM)	*p* value
N	200	65	135	
Demographics				
Age	35±12	41±11	32±10	**<.001**
Female (%)	72	60	78	**.01**
White (%)	76	72	77	.07
Education (%)				.57
<High school	14	18	12	
High school degree/equivalent	35	35	34	
Some college	40	37	41	
Associate degree or higher	12	9	13	
Employment (%)				**<.001**
Full-time work	25	15	30	
Part-time work	16	9	19	
Casual employment	8	8	8	
Unemployed	27	23	28	
Other	25	45	16	
Marital Status (%)				**<.01**
Never married	61	52	65	
Married	16	9	19	
Divorced or separated	21	34	14	
Widowed	3	5	1	
Smoking Characteristics				
Cigarettes/day	16±7	16±6	15±8	.06
Intake CO level	22±11	23±12	21±11	.33
Age started smoking regularly	16±4	16±5	16±3	.29
FTCD total score	4.9±2	5.3±2	4.7±2	**.03**
Menthol smoker (%)	35	35	34	.87
Psychiatric Characteristics				
BDI total score	12±11	8±8	14±13	**<.01**
OASIS total score	6±5	3±3	7±6	**<.001**
Opioid Treatment Characteristics				
Methadone maintained (%)		58		
Methadone dose, mg		97±30		
Buprenorphine dose, mg		14±9		

Note. Mean ± standard deviation unless otherwise noted; Bolded values represent $p<.05$; BDI, Beck Depression Inventory (Beck, 1996); OASIS, Overall Anxiety Severity and Impairment Scale (Norman et al., 2006); FTCD, Fagerström Test for Cigarette Dependence (Fagerström, 2012).

Table 3

Multivariable Models Predicting MTWS Total Scores at the Baseline Usual Brand Session (Session 1) and in Response to Cigarettes Varying in Nicotine Content (Sessions 2-5)

Final models (All significant predictors)				Final models (All significant predictors with OM status forced in)		
Variable	**F value**	***p* value**		**Variable**	**F value**	***p* value**
Session 1				*Session 1*		
Time	52.80	<.001		Time	52.80	<.001
BDI	39.69	<.001		BDI	43.98	<.001
FTCD	10.36	<.01		FTCD	9.01	<.01
				OM Status	2.62	.11
Sessions 2-5				*Sessions 2-5*		
Dose	3.65	.01		Dose	3.65	.02
Time	97.30	<.001		Time	97.30	<.001
Dose x Time	3.00	<.001		Dose x Time	3.00	<.01
BDI	28.23	<.001		BDI	36.94	<.001
Education	3.08	.03		Education	3.23	.03
FTCD	9.34	<.01		FTCD	5.98	.02
				Race	3.41	.04
				OM Status	6.65	.01

Table 4

Multivariable Models Predicting MTWS Desire to Smoke at the Baseline Usual Brand Session (Session 1) and in Response to Cigarettes Varying in Nicotine Content (Sessions 2-5)

Final models (All significant predictors)				Final models (All significant predictors with OM status forced in)		
Variable	**F value**	***p* value**		**Variable**	**F value**	***p* value**
Session 1				*Session 1*		
Time	62.82	<.001		Time	62.82	<.001
BDI	6.22	.01		BDI	6	.02
FTCD	26.39	<.001		FTCD	25.54	<.001
CO level	9.6	<.01		CO level	9.46	<.01
				OM status	0.04	.84
Sessions 2-5				*Sessions 2-5*		
Dose	8.77	<.001		Dose	8.77	<.001
Time	130.93	<.001		Time	130.93	<.001
Dose x Time	6.42	<.001		Dose x Time	6.42	<.001
FTCD	32.09	<.001		FTCD	32.09	<.001
OM status	0.88	.35		OM status	0.88	.35

Time x OM status	3.34	.01		Time x OM status	3.34	.01

Table 5

Multivariable Models Predicting MTWS Total and Desire to Smoke AUC Scores at the Baseline Usual Brand Session and in Response to Cigarettes Varying in Nicotine Content

MTWS Total Score AUC

Final models (All significant predictors)				Final models (All significant predictors with OM status forced in)		
Variable	**F value**	***p* value**		**Variable**	**F value**	***p* value**
Session 1				*Session 1*		
BDI	38.22	<.001		BDI	41.14	<.001
FTCD	12.10	<.01		FTCD	10.26	<.01
				OM status	2.61	.12
Sessions 2-5				*Sessions 2-5*		
Dose	3.85	<.01		Dose	3.85	<.01
BDI	36.70	<.001		BDI	36.70	<.001
FTCD	6.71	.01		FTCD	6.71	.01
Education	3.42	.02		Education	3.42	.02
OM status	5.58	.02		OM status	5.58	.02

MTWS Desire to Smoke AUC

Final models (All significant predictors)				Final models (All significant predictors with OM status forced in)		
Variable	**F value**	***p* value**		**Variable**	**F value**	***p* value**
Session 1				*Session 1*		
BDI	5.78	.02		BDI	5.79	0.02
FTCD	26.80	<.001		FTCD	25.74	<.001
CO level	8.21	<.01		CO level	8.04	<.01
				OM status	0.12	.73
Sessions 2-5				*Sessions 2-5*		
Dose	10.55	<.001		Dose	10.55	<.001
FTCD	34.83	<.001		FTCD	32.75	<.001
				OM status	0.94	.33

Table 6

Baseline Demographic and Smoking Characteristics of Phase 1 Completers vs. Noncompleters

	All	**Phase 1 Completer**	**Noncompleter**	***p* value**
N	235	200	35	
Demographics				
Age	34 ± 12	35± 11	31 ± 12	.10
Female (%)	73	72	77	.68
White (%)	77	75	86	.23
Education (%)				.27
<High school	13	14	6	
High school degree/equivalent	37	34	5	
Some college	39	40	34	
Associate degree or higher	11	11	9	
Employment (%)				.14
Full-time work	27	25	40	
Part-time work	14	15	3	
Casual employment	8	8	6	
Unemployed	27	26	31	
Other	24	25	20	
Marital Status (%)				.29
Never married	62	61	66	
Married	14	16	6	
Divorced or separated	22	20	29	
Widowed	2	2	0	
Smoking Characteristics				
Cigarettes/day	16 ± 7	15 ± 7	18 ± 7	**.05**
Intake CO level	22 ± 11	22 ± 11	21 ± 10	.81
Age started smoking regularly	16 ± 4	16 ± 4	16 ± 3	.35
FTCD total score	5 ± 2	5 ± 2	5 ± 2	.59
Menthol smoker (%)	34	34	31	.85

Note. Mean ± standard deviation unless otherwise noted*;* Continuous variables were tested using the Student's t-test; Categorical variables were tested using Fisher's Exact Test; Bolded values represent $p<.05$.

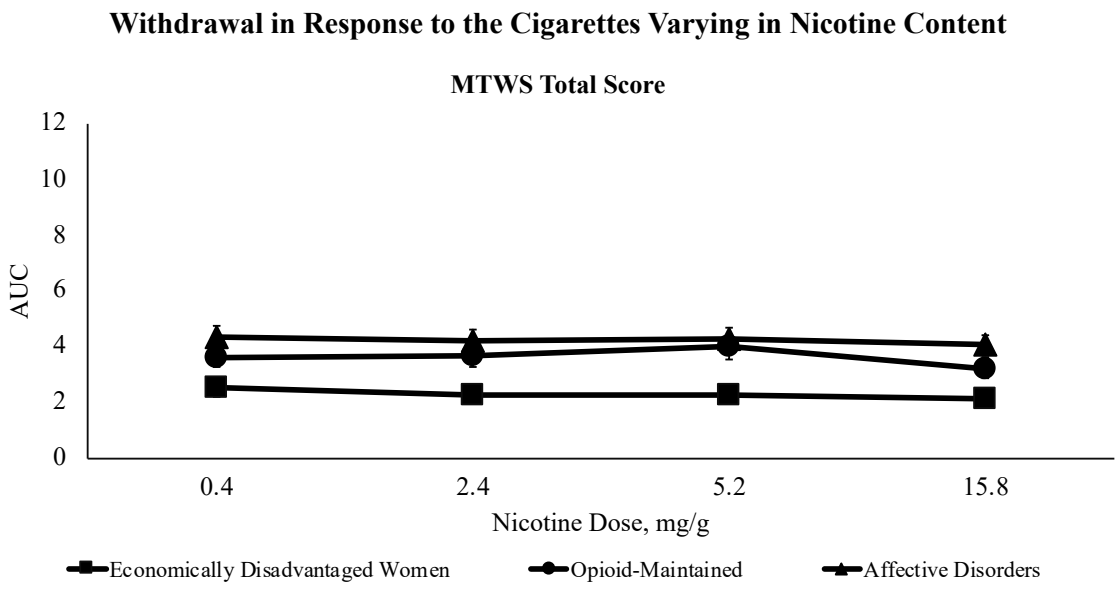

Figure 1. MTWS Total AUC scores from the parent study (Higgins et al., 2017), presented across nicotine doses by study sub-sample

Note. Error bars represent standard error of the mean.

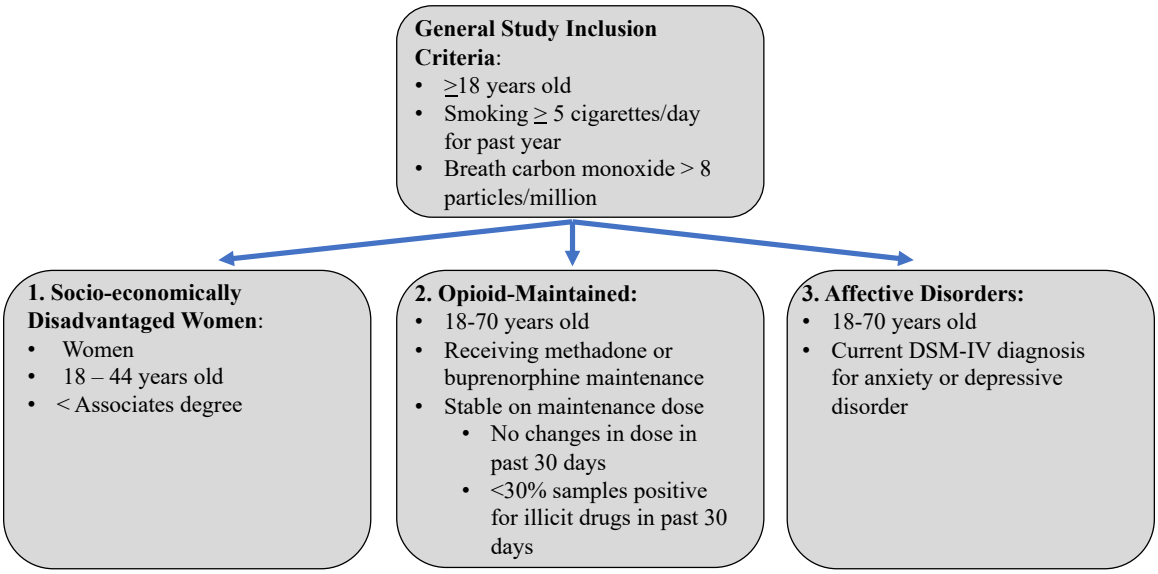

Figure 2. Inclusion criteria for the parent study sub-samples

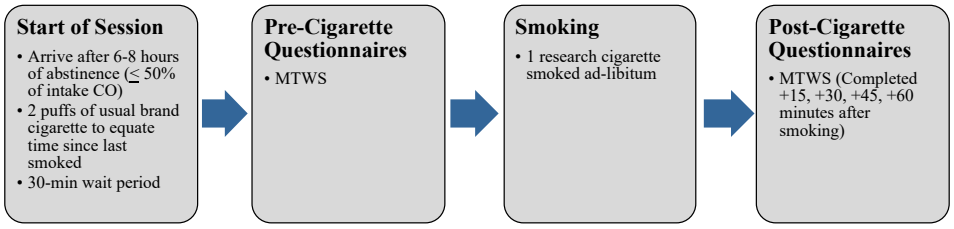

Figure 3. Overview of experimental procedures during baseline (Session 1) and Study Phase 1 (Sessions 2-5).

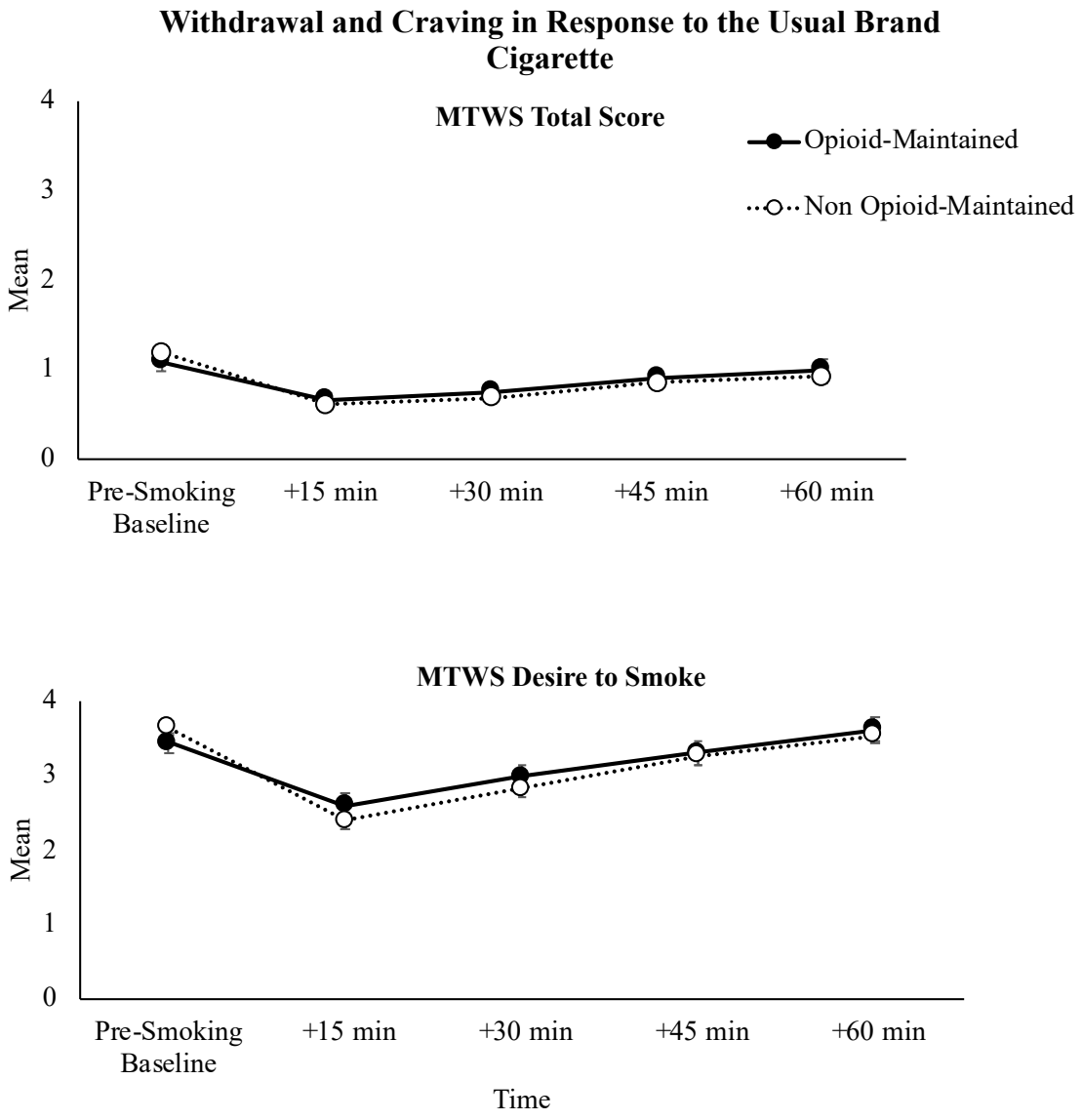

Figure 4. MTWS Total and Desire to Smoke scores at the baseline session across time by OM status

Note. Error bars represent standard error of the mean.

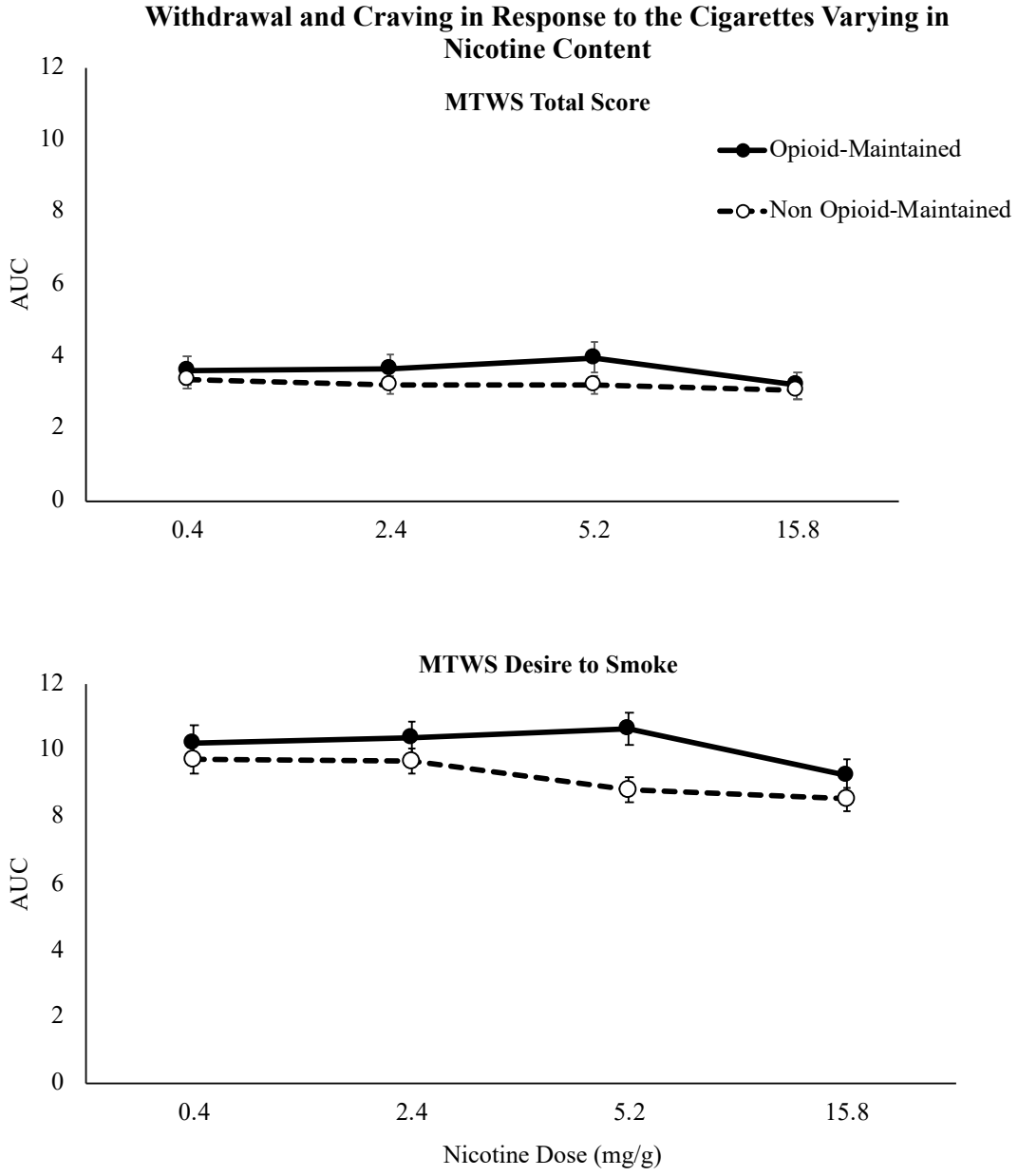

Figure 5. MTWS Total and Desire to Smoke AUC scores across nicotine dose by OM status

Note. Error bars represent standard error of the mean. To ease interpretation of Aim 2 data involving multiple nicotine doses and timepoints, AUC data are presented.

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